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WO 03/104233 A1

(54) Title: 4,5-DIHYDRO-IMIDAZO (4,5,1-IJ) QUINOLIN-6-ONES DERIVATIVES AND THEIR USE AS POLY (ADP-RIBOSYL) TRANSFERASE (PARP) INHIBITORS

(57) Abstract: Compounds of a certain formula 1, in which A has the meanings indicated in the description, are novel active PARP inhibitors.

4,5-DIHYDRO-IMIDAZO(4,5,1-IJ)QUINOLIN-6-ONES DERIVATIVES AND THEIR USE AS POLY(ADP-RIBOSYL)TRANSFERASE (PARP) INHIBITORS

Field of application of the invention

The invention relates to novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

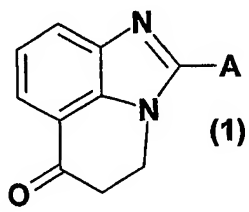
Known technical background

In the International patent applications WO00/42040, WO01/23386 and WO01/23390 3,4-Dihydro-1,2a,4-triaza-acenaphthylen-5-one derivatives are described as poly(ADP-ribosyl)transferase (PARP) inhibitors. In the European patent application EP 0405442 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described with hypotensive, anti-oedematous and diuretic effects. In the European patent application EP 0646583 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described as inhibitors for types 5-HT_3 and 5-HT_4 serotoninergic receptors. In the International patent application WO01/16136 8,9-Dihydro-7H-2,7,9a-triaza-benzo[cd]azulen-6-one derivatives are disclosed as poly(ADP-ribosyl)transferase (PARP) inhibitors; in this application 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are mentioned as possible intermediates. In the International patent application WO02/12239 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives which are substituted by piperazinyl- or piperidinyl groups are disclosed as poly(ADP-ribosyl)transferase (PARP) inhibitors.

Description of the invention

It has now been found that the novel 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-ones described in greater detail below have surprising and particularly advantageous properties.

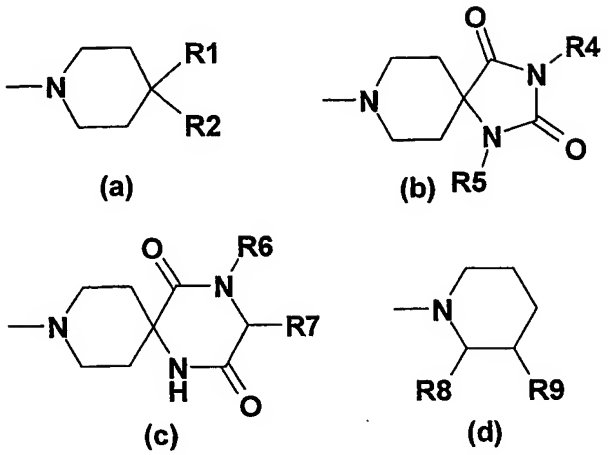
The invention thus relates to compounds of formula 1,



(1)

in which

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** either

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, di-1-4C-alkylaminocarbonyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl or

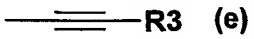
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)



(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 is acetoxy and

R2 a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

in **formula (b)**

R4 represents 4-fluorophenoxyethyl or
a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 is hydrogen or 1-4C-alkyl,

in **formula (c)** either

R6 is hydrogen or 1-4C-alkyl and

R7 is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxyeth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen,1-4C-alkyl and 1-4C-alkoxy,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)** either

R8 is 1-4C-alkoxycarbonyl and

R9 is hydrogen

or

R8 is hydrogen and

R9 is hydroxyl or hydroxymethyl,

the salts, the N-oxides and the salts of the N-oxides of these compounds,
and the following compounds
2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the above-mentioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, two of the abovementioned 1-4C-alkyl radicals. Preferred are the dimethylamino, the diethylamino and the diisopropylamino radical.

Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned di-1-4C-alkylamino radicals. Examples which may be mentioned are the N,N-dimethyl- and the N,N-diethyl-radical.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than the half of the hydrogen atoms of the 1-4C-alkoxy groups are replaced by fluorine atoms.

1-4C-Alkoxycarbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples are the methoxycarbonyl [CH_3O-C(O)-] and the ethoxycarbonyl [CH_3CH_2O-C(O)-] radical.

As 1-4C-Alkoxycarbonylamino radicals may be mentioned, for example, the methoxycarbonylamino, the ethoxycarbonylamino and the t-butoxycarbonylamino radical.

1-4C-Alkoxycarbonyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxycarbonyl radicals. An example is the methoxycarbonylmethyl radical [$CH_3OC(O)CH_2$-].

Halogen within the meaning of the present invention is bromine, chlorine and fluorine.

If R2 represents a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is substituted at one or more sites with a 1-4C-alkyl group, the 1-4C-alkyl group can be bonded to a carbon atom or can replace the hydrogen atom of a >NH radical. Examples which may be mentioned are N-1-4C-alkyl-pyrrolyl or N-1-4C-alkyl-pyrazolyl.

"N-oxides of these compounds" stands for any single or multiple N-oxide(s) which can be formed starting from the compounds of formula 1. Preferred are the single N-oxides.

Possible salts for compounds of the formula 1 - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

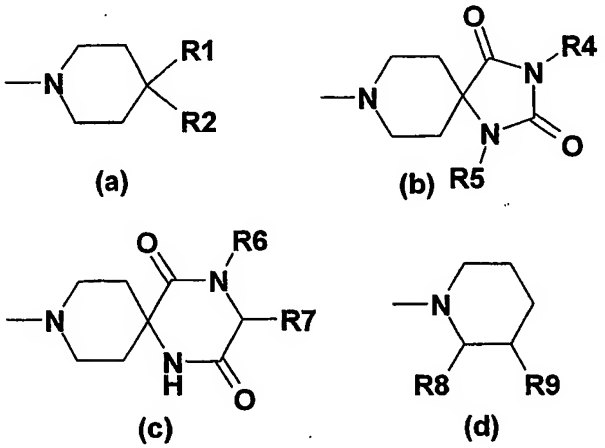
On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminum, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

One embodiment (embodiment A) of the invention are compounds of formula 1 in which
in which

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** either

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl

or

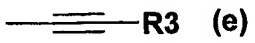
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)



(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 is acetoxy and

R2 a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

in **formula (b)**

R4 represents 4-fluorophenoxyethyl or
a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 is hydrogen or 1-4C-alkyl,

in **formula (c)** either

R6 is hydrogen or 1-4C-alkyl and

R7 is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxyeth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl,

phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen, 1-4C-alkyl and 1-4C-alkoxy,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)**

R8 is hydrogen and

R9 is hydroxymethyl,

the salts, the N-oxides and the salts of the N-oxides of these compounds,

and the following compounds

2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

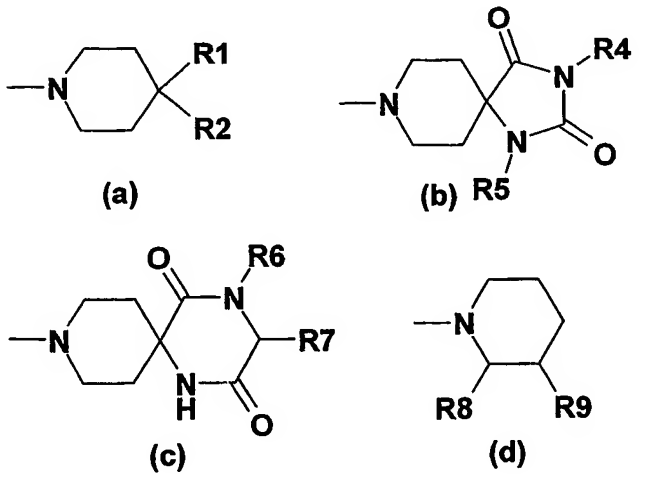
2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,

2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of the formula 1 to be emphasized are those in which

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** either

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, di-1-4C-alkylaminocarbonyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl or

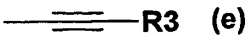
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)



(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 is acetoxy and

R2 a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

in **formula (b)**

R4 represents 4-fluorophenoxyethyl or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl,

1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 is hydrogen or 1-4C-alkyl,

in **formula (c)** either

R6 is hydrogen or 1-4C-alkyl and

R7 is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxy-eth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen,1-4C-alkyl and 1-4C-alkoxy,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)** either

R8 is 1-4C-alkoxycarbonyl and

R9 is hydrogen

or

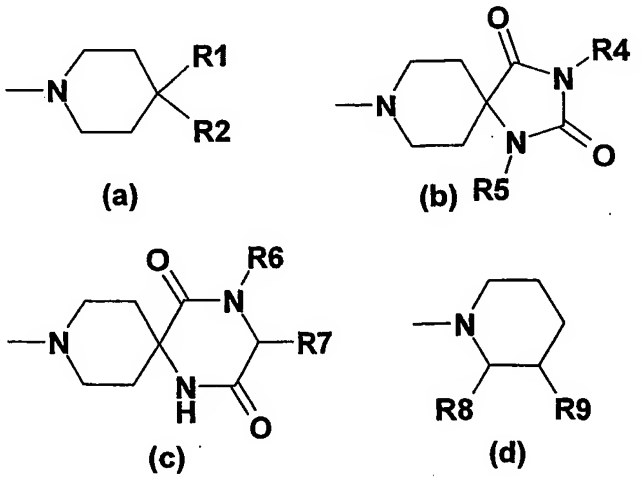
R8 is hydrogen and

R9 is hydroxyl or hydroxymethyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 of embodiment A which are to be emphasized are those in which

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** either

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl

or

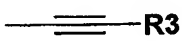
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)



(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 is acetoxy and

R2 a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

in **formula (b)**

R4 represents 4-fluorophenoxyethyl or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 is hydrogen or 1-4C-alkyl,

in **formula (c)** either

R6 is hydrogen or 1-4C-alkyl and

R7 is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxy-eth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen,1-4C-alkyl and 1-4C-alkoxy,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)**

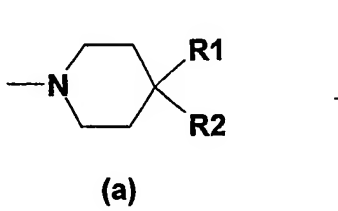
R8 is hydrogen and

R9 is hydroxymethyl,

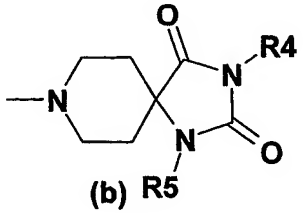
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of the formula 1 particularly to be emphasized are those in which

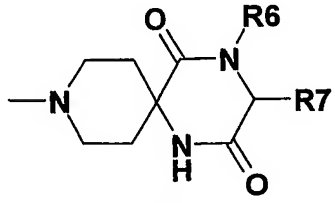
A represents a radical of formulae (a), (b), (c) or (d)



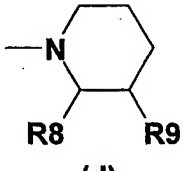
(a)



(b)



(c)



(d)

wherein

in **formula (a)** either

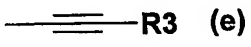
R1 is hydrogen and

R2 is hydroxyethyl, 3-methoxycarbonylbenzyl or thiophen-2-yl,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)



(e)

wherein

R3 is methoxymethyl, phenoxymethyl or tert-butyl,

in **formula (b)**

R4 is 3-fluorobenzyl, 4-fluorophenoxyethyl, 4-trifluoromethylbenzyl, 3-trifluoromethylphenyl or 3,5-dimethoxybenzyl, and

R5 is hydrogen,

in **formula (c)** either

R6 is hydrogen and

R7 is 1-4C-alkyl, 1-hydroxyeth-1-yl, phenyl or benzyl,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and in **formula (d)**

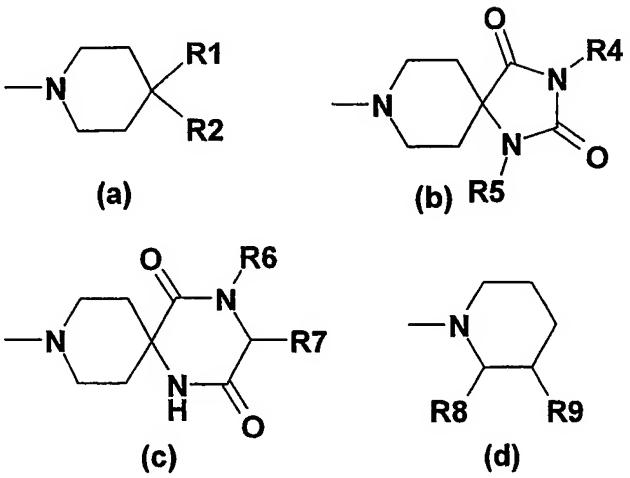
R8 is hydrogen and

R9 is hydroxyl or hydroxymethyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 of embodiment A which are particularly to be emphasized are those in which

A represents a radical of formulae (a), (b), (c) or (d)



wherein

in **formula (a)** either

R1 is hydrogen and

R2 is hydroxyethyl, 3-methoxycarbonylbenzyl or thiophen-2-yl,

or

R1 is hydroxyl and

R2 represents an alkynyl derivative of formula (e)

(e)

wherein

R3 is methoxymethyl, phenoxymethyl or tert-butyl,

in **formula (b)**

R4 is 3-fluorobenzyl, 4-fluorophenoxyethyl, 4-trifluoromethylbenzyl, 3-trifluoromethylphenyl or 3,5-dimethoxybenzyl, and

R5 is hydrogen,

in **formula (c)** either

R6 is hydrogen and

R7 is 1-4C-alkyl, 1-hydroxyeth-1-yl, phenyl or benzyl,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and in **formula (d)**

R8 is hydrogen and

R9 is hydroxymethyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds

Preferred compounds of the formula 1 are those in which

A is 3-(3-fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(4-trifluoromethylbenzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(3,5-dimethoxy-phenyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(4-fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-hydroxymethyl-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, 3-benzyl-1,4,9-triaza-2,5-dioxo-spiro-[5.5]undecan-9-yl, 3-isopropyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxyethyl-piperidin-1-yl, 4-propyl-piperidin-1-yl, 3-methyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 3-phenyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 3-(1-hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxy-pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-methoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-dimethyl-prop-1-ynyl)-piperidin-1-yl, 4-(thiophen-2-yl)-piperidin-1-yl, 4-(3-methoxycarbonyl-benzyl)-piperidin-1-yl, 4-hydroxyethyl-piperidin-1-yl or pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of formula 1 of embodiment A which are preferred are those in which

A is 3-(3-fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(4-trifluoromethylbenzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(3,5-dimethoxy-phenyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-(4-fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl, 3-hydroxymethyl-piperidin-1-yl, 3-benzyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 3-isopropyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxyethyl-piperidin-1-yl, 4-propyl-piperidin-1-yl, 3-methyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 3-phenyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 3-(1-hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxy-pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl, 4-hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-methoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-dimethyl-prop-1-ynyl)-piperidin-1-yl, 4-(thiophen-2-yl)-piperidin-1-yl, 4-(3-methoxycarbonyl-benzyl)-piperidin-1-yl, 4-hydroxyethyl-piperidin-1-yl or pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further preferred compounds are

2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,

2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Particularly preferred compounds of formula 1 are
2-(3-(3-Fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(3-(4-Fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl)-4,5-dihydro-imidazo-[4,5,1ij]quinolin-6-one,
2-(3-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(Pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(3-Benzyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxyethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(3-Methyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(3-(1-Hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-Hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
2-(4-(Thiophen-2-yl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1ij]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A special embodiment of the compounds according to the invention are compounds of formula 1, in which A represents a radical of formula (a).

Another special embodiment of the compounds according to the invention are compounds of formula 1, in which A represents a radical of formula (b).

Still another special embodiment of the compounds according to the invention are compounds of formula 1, in which A represents a radical of formula (c).

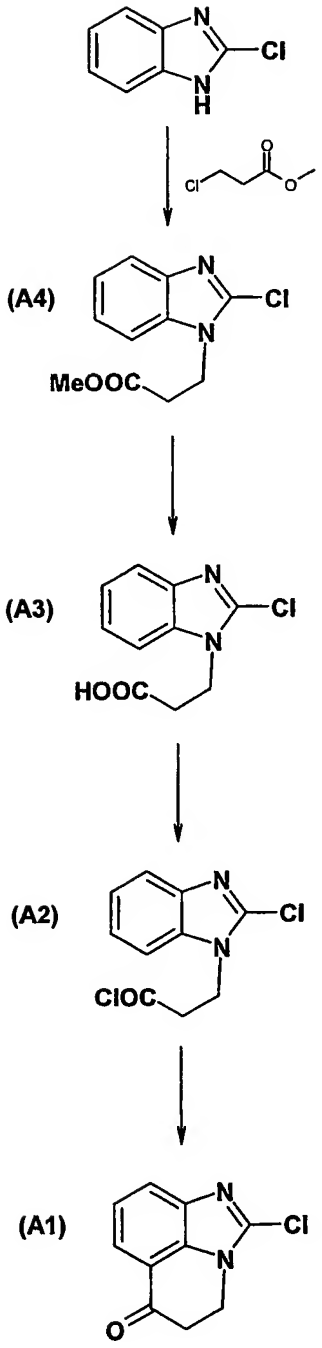
A further special embodiment of the compounds according to the invention are compounds of formula 1, in which A represents a radical of formula (d).

The preparation of the compounds of the formula 1 in which A has the meanings indicated above and their salts can be carried out, for example, by the processes described in greater detail below in the

reaction schemes 1 and 2. Reaction scheme 1 shows the preparation of the intermediate product A1. In a first reaction step intermediate product A4 is prepared by reacting 2-chloro-1H-benzimidazole with 3-chloropropionic acid methyl ester. The methyl ester of intermediate product A4 is then hydrolysed to give 3-(2-chloro-benzimidazol-4-yl)-propionic acid (intermediate product A3). Intermediate product A3 is then converted to the corresponding acid chloride A2. Finally, intermediate product A2 is cyclocondensed to give intermediate A1.

The starting compounds 2-chloro-1H-benzimidazole and 3-chloropropionic acid methyl ester are commercial available. The reaction conditions which, for example, can be applied for the preparation of the intermediate product A1 are described in the paragraph starting compounds and intermediate products.

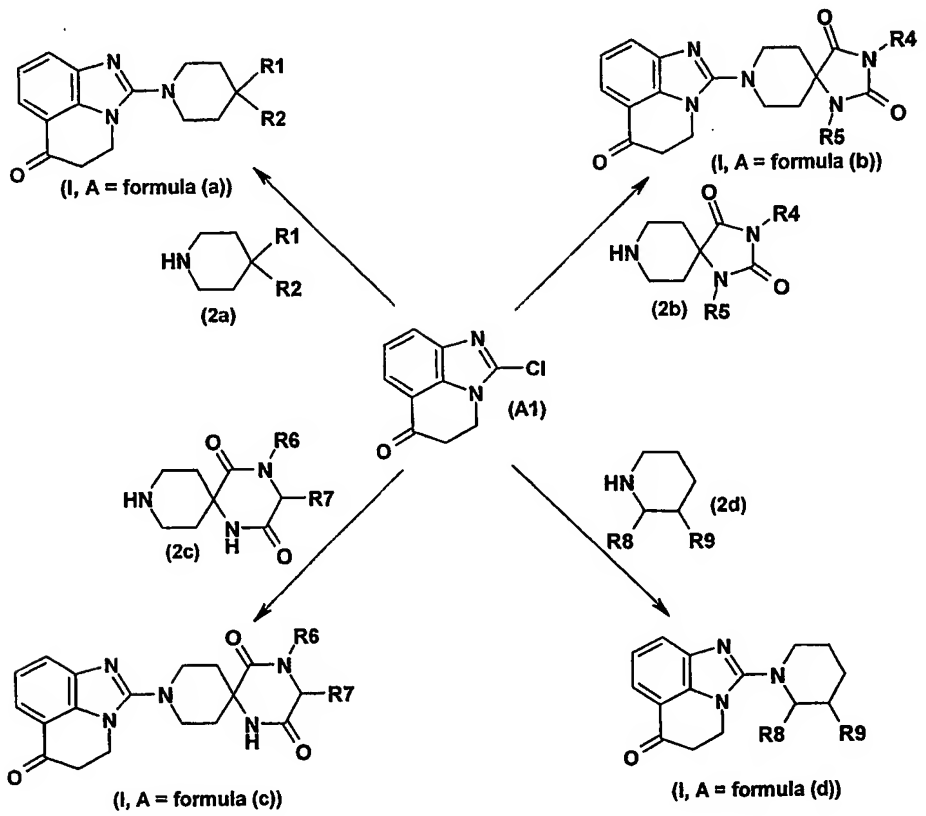
Reaction scheme 1:



In reaction scheme 2 the final step in the preparation of compounds of formula 1, wherein A represents a radical of formulae (a), (b), (c) or (d) is shown. Intermediate product A1 is reacted with compounds of the formulae (2a), (2b), (2c) or (2d) to give the compounds of formula 1.

Compounds of formulae (2a), (2b), (2c) or (2d) are known or can be prepared according to methods known to the person skilled in the art.

Reaction scheme 2:



The compounds of formula 1 prepared by the processes described above can, if desired, be converted into their salts, or salts of the compounds of formula 1 obtained can, if desired, be converted into the free compounds. Corresponding processes are known to the person skilled in the art.

In addition, the compounds of formula 1 can be converted by derivatisation into further compounds of formula 1. Thus, for example, compounds of formula 1 can be converted, if desired, into their N-oxides.

The N-oxidation is carried out in a manner which is known to the person skilled in the art, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is known to the person skilled in the art that in the case of a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula 1, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, h stands for hour(s), RT for room temperature, calc. for calculated, fnd. for found. MS stans for Atmospheric Pressure Chemical Ionisation Mass Spectrometry (APCI-MS) or Electron Impact Inoisation Mass Spectrometry (EI-MS). The compounds mentioned in the examples and their salts are a preferred subject of the invention.

Examples

Final products

1. **2-(3-(3-Fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4,5]-decane-8-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

42 mg of 2-Chloro-4,5-dihydro-imidazo[4,5,1-*ij*

2. **2-(3-(4-Trifluoromethylbenzyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

3. **2-(3-(3,5-Dimethoxyphenyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

4. **2-(3-(4-Fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro-[4.5]-decane-8-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

5. **2-(3-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one**

6. 2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

7. 2-(3-Benzyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

8. 2-(3-Isopropyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

9. 2-(3-Methyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

10. 2-(3-Phenyl-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

11. 2-(3-(1-Hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

12. 2-(4-Hydroxy-pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

13. 2-(4-Hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

14. 2-(4-Hydroxy-4-(3-methoxy-prop-1-ynyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

15. 2-(4-Hydroxy-4-(3-dimethyl-prop-1-ynyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

16. 2-(4-(Thiophen-2-yl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

17. 2-(4-(3-Methoxycarbonyl-benzyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

18. 2-(4-Hydroxyethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

19. 2-(Pyrrolo[1,2a]-1,4,9-triaza-2,5-dioxo-spiro[5.5]undecan-9-yl)-4,5-dihydro-imidazo[4,5,1-ij]-quinolin-6-one

i

20. 2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

21. 2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

22. 2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

23. 2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

24. 2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

25. 2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

26. 2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

27. 2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

i

Starting compounds and intermediate products

A1. 2-Chloro-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

A3

A2

δ

A3. 3-(2-Chloro-benzoimidazol-4-yl)-propionic acid

A4

δ

Determination of HPLC-Values:

min	%A	%B

<u>**Commercial applicability**</u>

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i i i i i i i i
i i i i i i i i (Ikai et al., J. Histochem. Cytochem. 11: 1261-1264, 1983) a t a sc i tio al e latio . -1 is hi hly e esse i the clei o cells a is a mem e o the ase e cisio e ai com le (-com le). ce acti ate y ama e a me ts, -1 cataly es the attachme t o to 1 - i o-se its to a a iety o clea otei s hich a e i ol e i e ai , i cl i histo es, to oisom-e ases, - olyme ases, -li ases a -1 itsel . is se as a so ce o - i ose. oly - i osylatio is tho ht to sta ili e the e io o the si le st a eak a to allo the e-c itme t o othe - e ai e ymes. Co s me is e e e ate y the se o 4 -molec les o e e y molec le o . te i te se a to- - i osylatio -1 ecomes e ati ely cha e a issociates om the .

hi h m e o st a eaks ca se y i lammato y me iato s, ischemia e e sio o othe stim li lea s to a massi e o e acti atio o -1. It has ee sho that o e acti atio o s es ecially -1 lea s to a imme iate co s m tio o cell la . h s, i t acell la , the s st ate o , a a e e lete y massi e acti atio a this e e y e letio is tho ht to e o e stim l s lea i to cell la ama e a cell eath.

It is ell k o that tem o a y o y e e i atio as o i sit atio s o ischemia a e e sio lea s to the e e atio o eacti e o y e s ecies hich alo e o i com i atio ith it ic o i e lea to massi e st a eaks. I a e o t to e ai these st a eaks -1 is o e acti ate , e-s lti i cell la a e letio , cell eath a o a ama e. I isolate o a systems s ch as hea t o skeletal m scle i hi itio imi ishes ischemia e e sio i ce tiss e am-a e (Thiemerman et al. PNAS 94,: 679-683, 1997) an contractile ys nction (Docherty et al. Br. J. Pharmacol. 127,: 1518-1524, 1999). Protection rom PA P me iate cell eath has een sho n in PA P-1 knock-o t mice in ario s in- i o mo els o cere ral an myocar ial ischemia re er sion inj ry. A massi e re ction o the necrotic area in the CNS as re orte in PA P-1-knock o t mice

a ter transient occl sion o the mi le cere ral artery. Protection rom myocar ial ischemia re er sion ama e as also seen in PA P-1 knock o t mice a ter transient coronary occl sion. In mo els o car- iac ischemia an myocar ial in arction PA P inhi itors re ce in arct si e. It has een sho n in myo- cytes that PA P inhi ition inhi its cell lar o y ati e ama e (Bowes et al. Br. J. Pharmacol. 124: 1760-1766, 1998).

Similarly, in mo els o retinal ischemia re er sion PA P inhi ition has een shown to re ce cell lar an or an ama e. Con irmin res Its are a aila le rom small molec le inhi itors o PA Ps in mo els o transient cere ral ischemia an transient retinal ischemia (Lam, Res. Com. Mol. Pathol. Pharmacol. 95, 241-252, 1997).

Similarly, ac te or chronic in lammation in eneral is characterise amon others y massi e enera- tion o reacti e o y en s ecies an nitric o i e. As in the case o ischemia re er sion these reacti e s ecies lea to DNA stran reaks, PARP-1 o eracti ation an cell eath. It has een shown that PARP inhi ition y small molec le inhi itors or enetic knock o t re ces e ema ormation a ter ymo- san or carra eenan, inhi its cell lar ama e in ancreatic islet cells a ter stre to otocin, inhi its e - erimental arthritis an re ces intestinal ama e in mo els o intestinal in lammation. i ence e ists that PARP inhi itors are se l or treatin in lammatory owel isor ers. (Salzman et al., Japanese J. Pharm., 75, Supp. I:15, 1997). In ro ent in i o mo els e perimentally in uce colitis was re uce y a ministration o PARP inhi itors.

i ence also e ists that PARP inhi itors are use ul or treatin arthritis. (Szabo et al., Japanese J. Pharm., 75, Supp. I:102, 1997). Besi e an inhibition o cellular ama e ue to the abo e mentione mechanisms it has been emonstrate that PARP inhibition re uces the e pression o proin lammatory a hesion molecules such as ICAM-1 an P-selectin.

It has also been reporte that PARP acti ation plays a key role in lutamate-, NMDA-, N -, reacti e o y en species- an lucose epri ation in uce neuroto icity. The use o PARP inhibitors was re- porte to pre ent neuroto icity in cortical or cerebellar ranule cell cultures an in hippocampal slices (Wallis et al., NeuroReport, 5:3, 245-48. 1993; Cosi et al, J. Neurosci. Res 39: 38-46, 1994; Eliasson et al. Nature Med. 3: 1089-1095, 1997); Inhibition o neuroto icity by arious compounds was ound to correspond to their PARP-1 inhibitory potency (Zhang et al., Science, 263.687-89, 1994); E cessi e acti ation o glutamate receptors has been implicated in arious neurological diseases. N together with reacti e o ygen species has been shown to be causally in ol ed in in- i o models or arious neu- rodegenerati e diseases o the CNS. During ischemia reper usion injury arious neuroto ic species including glutamate, N , reacti e o ygen species and others are released leading to massi e organ damage. ther pathophysiological stimuli resulting in PARP acti ation and concomittant cell damage are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), leading to e perimental parkinsonism, im- mune comple es mediating e perimental encephalomyelitis and traumatic head injury.

There are also data showing that PARP inhibitors reduce the se erity o septic or hemorrhagic shock in animal models. Sur i al o mice a ter a lethal dose o LPS was increased by PARP inhibitors (Szabo et al. Int. J. Oncology 10, 1093-1101, 1997). In addition organ dys unction (shown or lung, li er, intestine) a ter zymosan in e perimental models o shock is reduced by PARP inhibitors (Szabo et al. J.Exp. Med. 186, 1041-1049, 1997).

It has also been shown that PARP-1 inhibition protects pancreatic islet cells rom NO or reacti e oxygene species induced damage (Uchigata et al. J. Biol. Chem. 257 6084- 6088,1982). In more complex models o streptozotocin induced diabetes, PARP-1 inhibition reduced cellular damage and increased insulin production (Uchigata et al. Diabetes 32, 316-318, 1983)

PARP inhibitors ha e been reported to be e ecti e in radiosensitizing hypoxic tumor cells and in pre- enting tumor cells rom reco ering rom potentially lethal damage o DNA a ter radiation therapy, presumably by their ability to pre ent DNA repair (Griffin et al. J. Med. Chem. 41, 5247-5256, 1998).

On account of their PARP - in particular their PARP-1 - inhibiting properties, the compounds according to the in ention can be employed in human and eterinary medicine and therapeutics, where they can be used for the treatment and prophylaxis of the following diseases: ascular stroke (cerebral stroke), myocardial infarction and other cardio ascular disorders (artherosclerosis), diabetes, head trauma, sepsis and septic shock; hemorrhagic shock, tissue damage resulting from PARP-1 mediated necrosis or apoptosis; any kind of reperfusion injury; especially neuronal (CNS), myocardial, retinal or other tissue damage resulting from ischemia and reperfusion; ischemia reperfusion injury during organ transplantation surgery, surgery with transient interruption of blood flow to organs or body areas, and surgery when heart-lung heart-circulation machines are used; renal failure due to ischemia or glomerulonephritis, retinal ischemia; neurological disorders and neurodegenerati e diseases caused by free radical generation or other PARP-1 acti ating stimuli; pancreatic disorders; acute and chronic inflammatory diseases (chronic inflammatory disease of the CNS (Alzheimer, multiple sklerosis, Parkinson s disease), chronic inflammatory diseases of the gastrointestinal tract (Morbus Crohn, colitis ulcerosa), chronic inflammatory diseases of the lungs (acute lung injury, ARDS), chronic inflammatory diseases of the joints (rheumatoid arthritis, osteoarthritis), acute inflammatory diseases of arious organs; traumata of arious organs; iral infections which rely on PARP-acti ity for successful DNA integration; infections by human immune deficiency and other iruses (AIDS); degenerati e diseases of skeletal muscle in- ol ing replicati e senescence, immune senescence, muscular dystrophy, chronic and acute pain (neuropathic pain),and skin aging.

In addition to this, conditions including epilepsy, stroke, Alzheimer s disease, Parkinson s disease, Amyotrophic Lateral Sclerosis (ALS), Huntington s disease, schizophrenia, chronic pain, ischemia and neuronal loss following hypoxia, hypoglycemia, ischemia, trauma, and ner ous insult can be expected

to be mitigated by PARP-1 inhibition. Recent studies ha e also ad anced a glutamatergic basis for compulsi e disorders, particularly drug dependence.

urthermore PARP-inhibitors can be used to extend the lifespan and proliferati e capacity of cells; to alter gene expression of senescent cells and to enhance the efficacy of chemo- or radiotherapy in cancers. PARP-inhibitors can also be used to potentiate cellular necrosis and or apoptosis by chemotherapeutic compounds of arious classes.

The in ention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abo ementioned illnesses. The method is characterized in that a therapeutically acti e and pharmacologically effecti e and tolerable amount of one or more of the compounds according to the in ention is administered to the ill mammal.

The in ention further relates to the compounds according to the in ention for use in the treatment and or prophylaxis of illnesses, especially the illnesses mentioned.

The in ention also relates to the use of the compounds according to the in ention for the production of pharmaceutical compositions which are employed for the treatment and or prophylaxis of the illnesses mentioned.

The in ention furthermore relates to pharmaceutical compositions for the treatment and or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the in ention.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the in ention (acti e compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the acti e compound content ad antageously being between 0.1 and 95 and where, by the appropriate choice of the auxiliaries and or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the acti e compound and or to the desired onset of action can be achie ed.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his her expert knowledge. In addition to sol ents, gel formers, ointment bases and other acti e compound excipients, for example antioxidants, dispersants, emulsifiers, preser ati es, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the in ention may be performed in any of the generally accepted modes of administration a ailable in the art. Illustrati e examples of suitable modes of administration include intra enous, oral, nasal, parenteral, topical, transdermal and rectal deli ery. Oral and intra enous deli ery is preferred.

The pharmaceutical compositions according to the in ention are prepared by processes known per se. Dosage of the acti e compounds takes place in the order of magnitude customary for PARP inhibitors. Thus topical application forms (such as, for example, ointments) contain the acti e compounds in a concentration of, for example, 0.1-99 . or oral administration, e.g., the dosage that may be employed is from about 0.1 to about 100 mg kg body weight, with courses of treatment repeated at appropriate inter als.

Biological investigations

The potency of the compounds according to the in ention to inhibit PARP-1 acti ity is tested by measuring the auto-ADP-ribosylation reaction at the le el of partially purified human PARP-1. Cellular PARP-acti ity was measured by uantification of nuclear poly-ADP-ribose polymer.

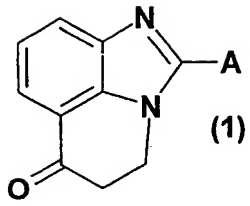
Measurement of enzymatic PARP-1 activity

100 ng of a crude cytosolic fraction of Sf9-cells expressing PARP-1 are incubated in a total olume of 200 l in the presence of 100 mM Tris HCl ph 7.4, 1 M NAD, 1.5 g Oligonucleotide (GGAATTCC) and 100000 to 200000 dpm of ^{3}H NAD for arious times. Radiolabelled poly-ADP-ribose is measured by adding 50 to 500 ng of an anti polyADP-ribose antibody or an anti-PARP-1 antibody linked to scintillation proximity beads (Protein-A-beads, Amersham-Pharmacia). Bead bound radioacti ity is measured in a Wallac Trilux Microbeta counter. Inhibition of PARP acti ity by compounds is calculated from control alues in the absence of compounds and IC_{50}- alues (concentration of compound yielding 50 inhibition are generated by nonlinear least s uare fitting.

The inhibitory alues measured as -logIC_{50} (mol l) determined for the compounds 1 to 27 were all greater than 5. The number of the compounds correspond to the number of the examples.

Patent claims

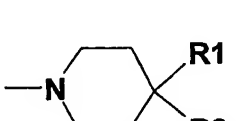
1. *A compound of formula 1,*



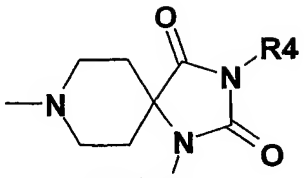
(1)

in which

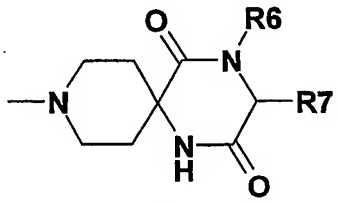
A represents a radical of formulae (a), (b), (c) or (d),



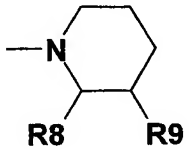
(a)



(b)



(c)



(d)

wherein

in **formula (a)** *either*

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, di-1-4C-alkylaminocarbonyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl or

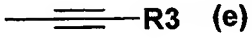
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 *represents an alkynyl deri ati e of formula (e)*



(e)

wherein

R3 *is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,*

or

R1 *is acetoxy and*

R2 *a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

or

R1 *is hydroxyl and*

R2 *a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

in **formula (b)**

R4 *represents 4-fluorophenoxyethyl or*
a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 *is hydrogen or 1-4C-alkyl,*

in **formula (c)** *either*

R6 *is hydrogen or 1-4C-alkyl and*

R7 *is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxyeth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen, 1-4C-alkyl and 1-4C-alkoxy,*

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)** *either*

R8 is 1-4C-alkoxycarbonyl and

R9 is hydrogen

or

R8 is hydrogen and

R9 is hydroxyl or hydroxymethyl,

or a salt, a N-oxide or a salt of the N-oxide thereof,

or a compound selected from

2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

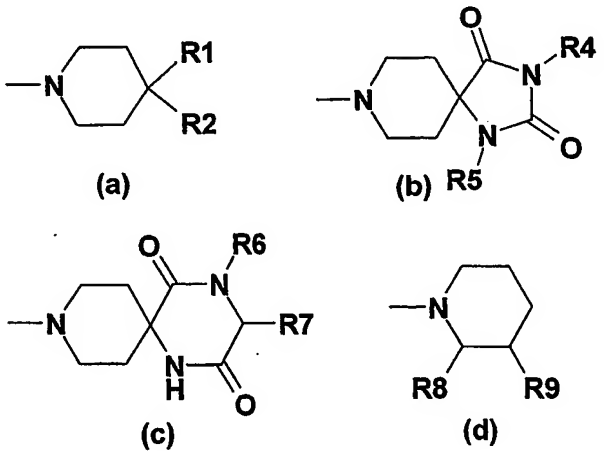
2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one,

or a salt, a N-oxide or a salt of the N-oxide thereof.

2. *A compound of formula 1 as claimed in claim 1, in which*

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** *either*

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 *is hydrogen and*

R2 *represents hydroxyethyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl*

or

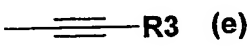
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 *is hydroxyl and*

R2 *represents an alkynyl deri ati e of formula (e)*



(e)

wherein

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or

R1 *is acetoxy and*

R2 *a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

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R5 is hydrogen or 1-4C-alkyl,

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R7 is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxy-eth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen, 1-4C-alkyl and 1-4C-alkoxy,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)**

R8 is hydrogen and

R9 is hydroxymethyl,

or a salt, a N-oxide or a salt of the N-oxide thereof,

or a compound selected from

2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,

2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one,

2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one,

or a salt, a N-oxide or a salt of the N-oxide thereof.

3. *A compound of formula 1 as claimed in claim 1, in which*

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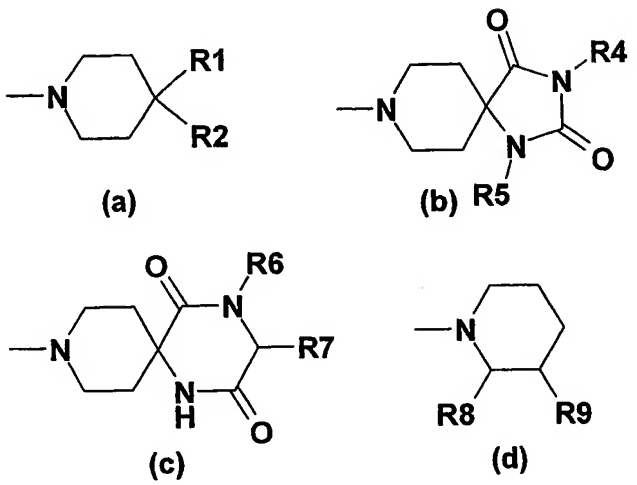

wherein

in **formula (a)** *either*

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or

R1 is hydrogen and

R2 represents hydroxyethyl, di-1-4C-alkylaminocarbonyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl or

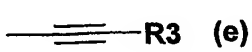
a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl deri ati e of formula (e)



(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 is acetoxy and

R2 *a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

or

R1 *is hydroxyl and*

R2 *a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

in **formula (b)**

R4 *represents 4-fluorophenoxyethyl or*
a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 *is hydrogen or 1-4C-alkyl,*

in **formula (c)** *either*

R6 *is hydrogen or 1-4C-alkyl and*

R7 *is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxyeth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen, 1-4C-alkyl and 1-4C-alkoxy,*

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)** *either*

R8 *is 1-4C-alkoxycarbonyl and*

R9 *is hydrogen*

or

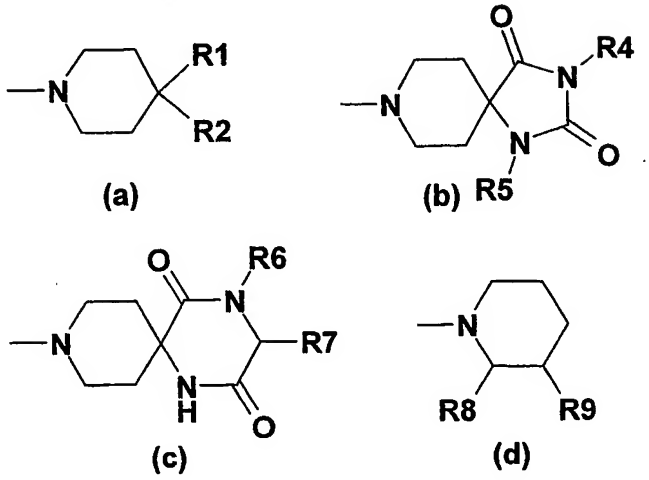
R8 *is hydrogen and*

R9 *is hydroxyl or hydroxymethyl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

4. *A compound of formula 1 as claimed in claim 1, in which*

A represents a radical of formulae (a), (b), (c) or (d),



wherein

in **formula (a)** *either*

R1 and R2 together with the carbon atom to which they are attached represent a carbonyl group,

or

R1 is hydrogen and

R2 represents hydroxyethyl, pyrrolidine-2-on-3-yl, 4-fluorophenylcarbonyl, 4-methoxyphenylcarbonyl

or

a thiophenyl, furanyl, benzimidazolyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl or triazinyl group which is unsubstituted or substituted at one or more sites with 1-4C-alkyl, or

a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

or

R1 is hydroxyl and

R2 represents an alkynyl deri ati e of formula (e)

(e)

wherein

R3 is phenyl, pyridyl, hydroxymethyl, methoxymethyl, phenoxymethyl, dimethylaminomethyl, tert-butyl, cyclopentylmethyl or 1-hydroxyeth-1-yl,

or

R1 *is acetoxy and*

R2 *a phenyl or benzyl group which is unsubstituted or substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

or

R1 *is hydroxyl and*

R2 *a benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of hydroxyl, hydroxymethyl, hydroxyethyl, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,*

in **formula (b)**

R4 *represents 4-fluorophenoxyethyl or*
a phenyl or benzyl group which is substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of 1-4C-alkyl, 1-4C-alkoxy, halogen, hydroxyl, hydroxymethyl hydroxyethyl, amino, mono- or di-1-4C-alkylamino, aminocarbonyl, 1-4C-alkoxy which is completely or predominantly substituted by fluorine, 1-4C-alkoxycarbonyl and 1-4C-alkoxycarbonylamino,

R5 *is hydrogen or 1-4C-alkyl,*

in **formula (c)** *either*

R6 *is hydrogen or 1-4C-alkyl and*

R7 *is hydrogen, 1-4C-alkyl, cyclohexyl, cyclohexylmethyl, methoxymethyl, hydroxymethyl, 1-hydroxyeth-1-yl, methylthioethyl, pyrid-4-yl, pyrid-3-yl, thiophen-2-yl, thiophen-3-yl, thiophen-2-ylmethyl, pyrid-2-ylmethyl, pyrid-3-ylmethyl, pyrid-4-ylmethyl, indan-3-ylmethyl, aminocarbonylmethyl, hydroxycarbonylmethyl, aminocarbonylethyl, hydroxycarbonylethyl, 1-4C-alkoxycarbonyl-1-4C-alkyl, phenyl, benzyl, or benzyl substituted by one or more identical or different substituents, where the substituents are selected from the group consisting of halogen,1-4C-alkyl and 1-4C-alkoxy,*

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and **in formula (d)**

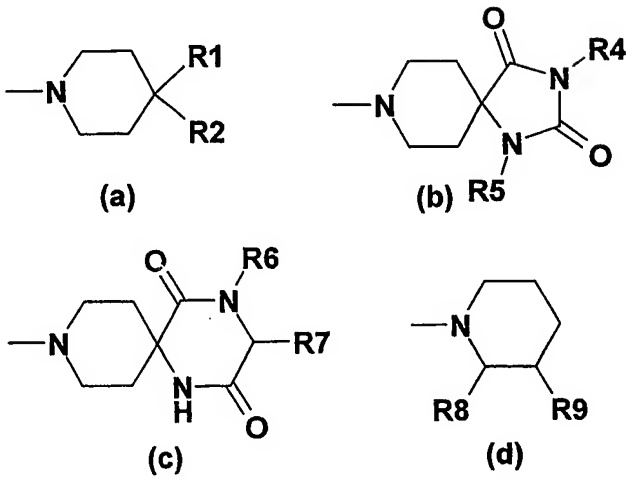
R8 *is hydrogen and*

R9 *is hydroxymethyl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

5. *A compound of formula 1 as claimed in claim 1, in which*

A represents a radical of formulae (a), (b), (c) or (d)



wherein

in **formula (a)** *either*

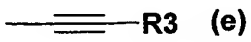
R1 is hydrogen and

R2 is hydroxyethyl, 3-methoxycarbonylbenzyl or thiophen-2-yl,

or

R1 is hydroxyl and

R2 represents an alkynyl deri ati e of formula (e)



(e)

wherein

R3 is methoxymethyl, phenoxymethyl or tert-butyl,

in **formula (b)**

R4 is 3-fluorobenzyl, 4-fluorophenoxyethyl, 4-trifluoromethylbenzyl, 3-trifluoromethylphenyl or 3,5-dimethoxybenzyl, and

R5 is hydrogen,

in **formula (c)** *either*

R6 is hydrogen and

R7 is 1-4C-alkyl, 1-hydroxyeth-1-yl, phenyl or benzyl,

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and in **formula (d)**

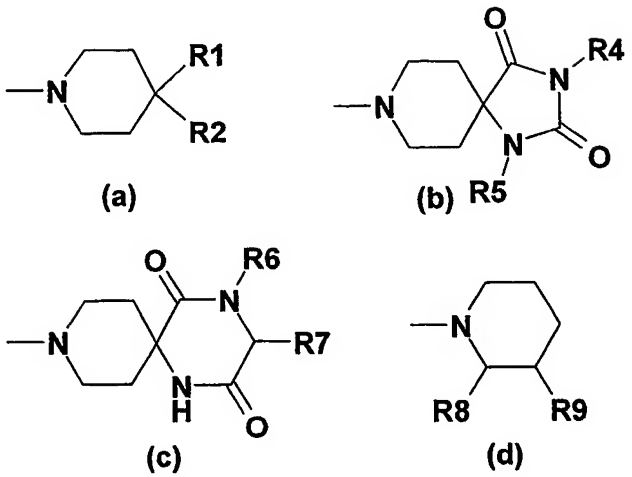
R8 *is hydrogen and*

R9 *is hydroxyl or hydroxymethyl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

6. *A compound of formula 1 as claimed in claim 1, in which*

A *represents a radical of formulae (a), (b), (c) or (d)*



wherein

in **formula (a)** *either*

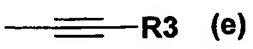
R1 *is hydrogen and*

R2 *is hydroxyethyl, 3-methoxycarbonylbenzyl or thiophen-2-yl,*

or

R1 *is hydroxyl and*

R2 *represents an alkynyl deri ati e of formula (e)*



(e)

wherein

R3 *is methoxymethyl, phenoxymethyl or tert-butyl,*

in **formula (b)**

R4 *is 3-fluorobenzyl, 4-fluorophenoxyethyl, 4-trifluoromethylbenzyl, 3-trifluoromethylphenyl or 3,5-dimethoxybenzyl, and*

R5 *is hydrogen,*

in **formula (c)** *either*

R6 *is hydrogen and*

R7 *is 1-4C-alkyl, 1-hydroxyeth-1-yl, phenyl or benzyl,*

or

R6 and R7 together with the nitrogen and the carbon atom to which they are attached form a pyrrolidine or a 3-hydroxypyrrolidine ring,

and in **formula (d)**

R8 *is hydrogen and*

R9 *is hydroxymethyl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

7. *A compound of formula 1 as claimed in claim 1, in which*

A *is 3-(3-fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(4-trifluoromethylbenzyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(3,5-dimethoxy-phenyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(4-fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-hydroxymethyl-piperidin-1-yl, 3-hydroxy-piperidin-1-yl, 3-benzyl-1,4,9-triaza-2,5-dioxo-spiro-5.5 undecan-9-yl, 3-isopropyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-hydroxyethyl-piperidin-1-yl, 4-propyl-piperidin-1-yl, 3-methyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 3-phenyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 3-(1-hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-Hydroxy-pyrrolo 1,2a -1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-methoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-dimethyl-prop-1-ynyl)-piperidin-1-yl, 4-(thiophen-2-yl)-piperidin-1-yl, 4-(3-methoxycarbonyl-benzyl)-piperidin-1-yl, 4-hydroxyethyl-piperidin-1-yl or pyrrolo 1,2a -1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

8. *A compound of formula 1 as claimed in claim 1, in which*

A *is 3-(3-fluoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(4-trifluoromethylbenzyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(3,5-dimethoxy-phenyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-(4-fluoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl, 3-hydroxymethyl-piperidin-1-yl, 3-benzyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 3-isopropyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-hydroxyethyl-piperidin-1-yl, 4-propyl-piperidin-1-yl, 3-methyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 3-phenyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 3-(1-hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-Hydroxy-pyrrolo 1,2a -1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl, 4-hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-methoxy-prop-1-ynyl)-piperidin-1-yl, 4-hydroxy-4-(3-dimethyl-prop-1-ynyl)-piperidin-1-yl, 4-(thiophen-2-yl)-piperidin-1-yl, 4-(3-methoxycarbonyl-benzyl)-piperidin-1-yl, 4-hydroxyethyl-piperidin-1-yl or pyrrolo 1,2a -1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl,*

or a salt, a N-oxide or a salt of the N-oxide thereof.

9. *A compound of formula 1 as claimed in claim 1 selected from*
2-(3-(3- luoro-benzyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(3-(4- luoro-phenoxy-ethyl)-1,3,8-triaza-2,4-dioxo-spiro- 4.5 -decane-8-yl)-4,5-dihydro-imidazo-4,5,1ij uinolin-6-one,
2-(3-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(Pyrrolo 1,2a -1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(3-Benzyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxyethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(3-Methyl-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(3-(1-Hydroxy-ethyl)-1,4,9-triaza-2,5-dioxo-spiro 5.5 undecan-9-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxy-4-(3-phenoxy-prop-1-ynyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one and
2-(4-(Thiophen-2-yl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
and the salts, the N-oxide and the salts of the N-oxide of this compound.

10. *A compound as claimed in claim 1 selected from*
2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one,
and the salts, the N-oxide and the salts of the N-oxide of this compound.

11. *A compound as claimed in claim 2 selected from*
2-(4-Methoxycarbonyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Propyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-(3-Methoxy-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxymethyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-(3-Trifluoromethyl-phenyl)-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-Hydroxy-4-benzyl-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1ij uinolin-6-one,
2-(4-tert-Butyloxycarbonylamino-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one,

2-(3-Hydroxy-piperidin-1-yl)-4,5-dihydro-imidazo 4,5,1-ij uinolin-6-one, or a salt, a N-oxide or a salt of the N-oxide thereof.

12. *A compound of formula 1 as claimed in claim 1 for use in the treatment of illnesses.*

13. *A medicament comprising at least one compound of formula 1 as claimed in claim 1 together with customary pharmaceutical excipients and or ehicles.*

14. *Use of a compound of formula 1 as claimed in claim 1 for the production of pharmaceutical compositions for the treatment of cancer, inflammation, ischemia reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.*

15. *A compound as claimed in the claims 10 or 11 for use in the treatment of illnesses.*

16. *A medicament comprising a compound as claimed in the claims 10 or 11 together with customary pharmaceutical excipients and or ehicles.*

17. *Use of a compound as claimed in claims 10 or 11 for the production of pharmaceutical compositions for the treatment of cancer, inflammation, ischemia reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.*

18. *A method of treating cancer, inflammation, ischemia reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct or diabetes mellitus in a patient, comprising administering to said patient a therapeutically effecti e amount of a compound of formula 1 as claimed in claim 1.*

19. *A method of treating cancer, inflammation, ischemia reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct or diabetes mellitus in a patient, comprising administering to said patient a therapeutically effecti e amount of a compound as claimed in the claims 10 or 11.*

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05834

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/06 C07D519/00 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 12239 A (BOLKENIUS FRANK ;SANOFI SYNTHELABO (FR); BARTH FRANCIS (FR); BICHO) 14 February 2002 (2002-02-14) cited in the application page 40, line 1-27 examples 1,28,36-48,54,61,62,64,77 claim 1 ---	1-19
A	EP 0 646 583 A (SYNTHELABO) 5 April 1995 (1995-04-05) cited in the application examples 16,17 ---	1-19
A	DE 100 39 610 A (BASF AG) 28 February 2002 (2002-02-28) claim 1 -----	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 2003	29/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Samsam Bakhtiary, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05834

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